THE LAW OF ACCELERATING RISK IN CANCER.[1]

A MATHEMATICAL FORMULA FOR CALCULATING THE EXPECTANCY AND POST-OPERATIVE PROGNOSIS OF MALIGNANT GROWTHS.

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Is there a Mathematical Law of Growth?—Cancer invades, conquers, and destroys the body of its victim, not by uniform or arithmetical progression, but in a geometrical or constantly accelerating ratio of progress. The late stages are manifold more rapid than the early stages. In an effort to state this law mathematically, I will consider the rate of progression and risk of recurrence as synonymous terms, and advance the following theorem:

1. *The risk of recurrence (or rate) in malignant growths increases as the square of the time of growth; or, conversely,*

2. *The risk of recurrence diminishes in the ratio of the square root of the time after incidence.*

Thus, doubling the time increases the risk of recurrence or metastases, not twice, but 2^2, or fourfold; tripling the time increases the risk 3^2, or ninefold; quadrupling the time increases it sixteen-fold, etc.

Because vital processes are difficult to measure, and because the exact age of a growth is not always known, it may not be easy to demonstrate this law mathematically; but it seems to coincide exactly with my clinical estimates of cases, and I cite the following reasons for believing in its accuracy:

Fundamental Conceptions.—Malignant tumors spread, not in a linear dimension, but centrifugally, from their atria in all directions, like an enlarging circle, or even a sphere. It

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is very rare for a growth to be so terminal as to spread in only one direction. This might possibly be true of a growth on a finger-tip, but would be temporary and exceptional. As an instance of radiating infection, a breast cancer invades quickly the axillary, cervical, and mediastinal lymph nodes; but it also soon involves the fascia down the chest to the abdominal wall, thus reaching the liver (Handley), or the skin and muscle across to the other breast (Heidenhain). Also it involves the lymph channels, following the intercostal vessels to the spine, causing skeletal deposits and cord lesions (paraplegia in several of my cases). It also invades the pleura along the line of the lymphatics, the perforating vessels, or muscles, and thus directly attacks the chest organs in some cases. In other words, it has about as many avenues of invasion as there are tissues surrounding it, and even the vascular system may aid in its dissemination.

Stated mathematically, the infection radiates in a sphere, with the primary focus as a centre. Like light, heat, and all radiations, it follows the law of squares. The superficial area, which is an index of the risk of metastasis, increases as the square of the diameter of the infected area. If a uniform growth in diameter takes place in a uniform time, then multiplying time by 2 would increase risk 4 times; multiplying time by 3 would increase risk 9 times; multiplying time by 4 would increase risk 16 times; multiplying time by 5 would increase risk 25 times; multiplying time by 10 would increase risk 100 times.

This soon brings us to infinite risk in finite time. In other words, a comparatively short time suffices to make every case infinitely dangerous or practically hopeless. This only restates theoretically what every surgeon knows to be mournful truth clinically.

What we lack to confirm this law clinically is means of locating the exact time of origin of any case. Theoretically, it is the date when the growth crossed the line between the microscopic and the macroscopic period. Practically, it is the accidental time of discovery of a neoplasm,—early in

accessible and exposed tissues, later in more concealed parts; perhaps never discovered before death in certain remote or unusual locations, as in the brain, prostate, or skeletal deposits.

The Law not a Death Warrant.—Discouraging as this law is when stated in its first or positive form, we may derive much comfort from the second or converse proposition as given above.

"*The risk of recurrence diminishes in the ratio of the square root of the time after incidence.*"

The law thus stated admonishes us that an early golden period is always given us for saving the life of the cancer victim, and imperatively commands us to take action during the brief and precious stage. We should look almost reverentially on the opportunity which then exists.

It is this curable stage only which is of strategic importance in surgery. Just what are its limits? Looking at the life history of any malignant case, we may consider it as composed of three periods: 1. The microscopic period. 2. The macroscopic period, before metastases. 3. Period after metastases or carcinosis period.

Of the first or microscopic period we know nothing except by inference.

For the carcinosis period we have little to offer therapeutically, save the hope that the X-ray, or some remedy yet unknown, may come as a sort of *deus ex machina* to the rescue.

Of the second stage, that of tumor building without metastases, we think we have abundant clinical evidence. Radical surgery should be mainly limited to this stage. By the law I have attempted to prove, I have obtained a working formula which, when applied clinically, will determine for us not perhaps the exact time limits within which it is safe to operate, but, at any rate, certain limits beyond which it is useless to operate for radical extirpation. As the conclusions arrived at have something of the authority of a law of nature, I will describe a little more fully the mode of demonstrating them by what I have ventured to call the "Risk Curve" plotted on a clinical chart.

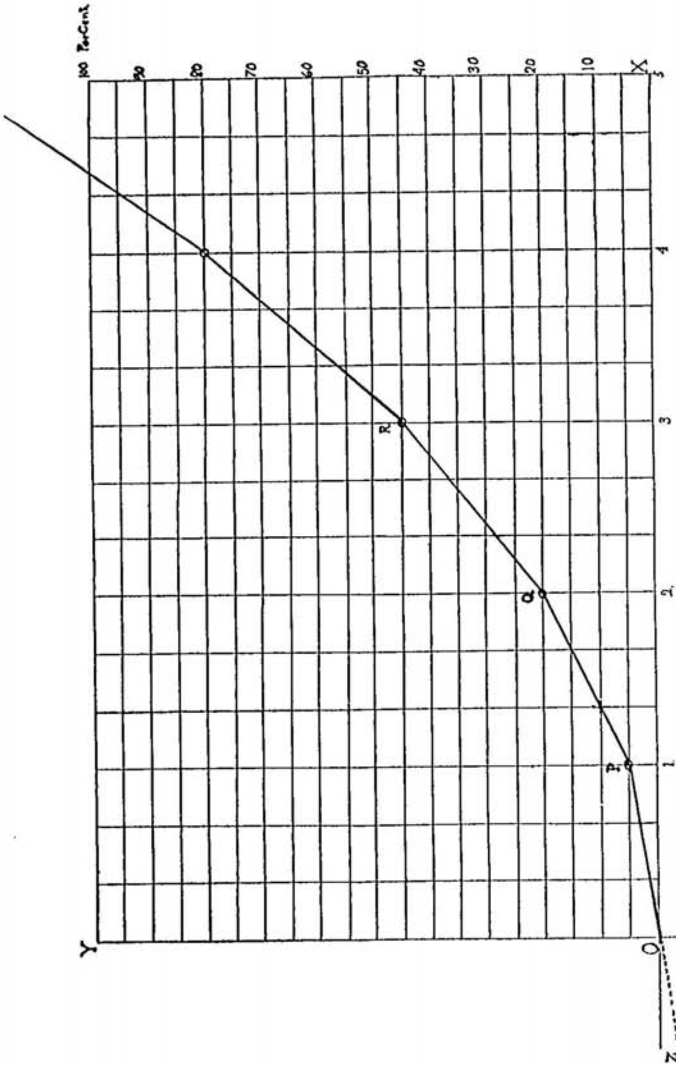

FIG. 1.—The risk curve in carcinoma. 1, 2, 3, etc., time elapsed. 10, 20, 30, etc., per cent. of risk. O P Q, "risk curve."

How to Plot the "Risk Curve."—The risk curve expressing mathematically the life chances of the patient is a function of two variable elements, viz., the rate of increase and the total age of the disease.

The coördinates *ax* and *oy* represent respectively the length or duration of the disease and the risk or probability of metastases. I have given a value to the abscissæ of 1, 2, 3, 4, 5, etc., representing time units, say of weeks or months, as we choose to assign them. The ordinates, 5, 10, 20, 30, 40, etc., stand for units of risk, say in parts of a hundred or percentages, 100 being a total of risk or a hopeless case, so that the higher risk lines are the ordinates above and the lower risk lines those below. We thus have a blank chart or scale marked in squares in two directions. Starting from *o* and moving upward, we enter various zones, or if you will planes, of risk, of values from zero to 100 per cent. Moving to the right, along *ox*, we cross the time abscissæ, which we give various values in different cases, so as to bring the life history of the disease into the compass of the card. The points, *o*, *p*, *q*, may now be located by the law of squares I have stated. Then the line, *o*, *p*, *q*, etc., will form a gently rising curve, at first nearly parallel to the base line, *ox*, thus remaining for a considerable time in a safe region, and afterwards rising sharply into a region of greater and greater risk, until after a certain period it is nearly vertical and crosses an increasing number of risk lines in each time space.

The dotted line, *zo*, represents the microscopic or previsible stage of the growth (if such a stage exist). At a certain time it crosses the base line ordinate at *o*, and becomes a visible or cognizable entity, thus entering on its life history, *o*, *p*, *q*, etc. At the theoretical first point of existence, its risk is *nil.* The lapse of the smallest amount of time carries it gradually above the base line, into an increasing danger zone.

To be able to plot the curve *o*, *p*, *q*, it is necessary to have data of the growth rate. This implies a knowledge from two examinations or a reliable history of how long it takes the mass, say, to double in size. I find it convenient to assign this time ratio to the space, 1, 2, 3; that is, if, a growth is known

to double in size in a month, the abscissæ represent months, etc.

Having fixed this index factor, the curve can be plotted by the law of squares I have already explained, and can be made to predict the future course of any case with great accuracy, so much so that I trust it in deciding the question for or against operating upon bad cases.

At the end of one time unit the risk rises to line $1 = 1$; in two units, to $2^2 = 4$; in 3 units of time to 3^2 or 9, and in 4 time units to 4^2 or 16, etc.

The percentages of increase will be the same in all cases. Only one factor varies, namely, the value of 0, 1, 2, 3, etc. It would be possible, therefore, to use one plotted curve for all cases by assigning different values to these time units. We can, on the other hand, represent graphically a slow or a rapid case by different curves by lengthening the time units proportionately to the rapidity found. Several curves can in this way be plotted on the same chart to contrast their rate of growth.

In whichever way we use the chart, we can lay down with fair accuracy the whole life history of the case, past, present, and future. I believe this will prove not only instructive and impressive for illustration, but accurate in prophesying the course and duration of tumors, if only our first data are reliable.

Clinical Test of the Law.—On the chart, two extreme cases, one extraordinarily rapid and the other unusually slow, both of which illustrate its accuracy, can be represented by the line, *o*, *p*, *q*, etc.

CASE I.—Miss M., aged forty-seven years, robust and well in appearance, had in November, 1894, a small movable nodule, size one-half inch, in right breast. Known duration, three weeks. I gave a bad prognosis, but allowed a delay of one week for observation. Patient, however, waited six weeks, and consulted me in January, with the tumor increased sixfold, and already some glands in axilla. I estimate the growth at fully 100 per cent. weekly, and it proved to be the most rapidly malignant carcinoma mammæ I ever saw.

Plotting the curve of this case on the basis of a doubling

each week, we have the extraordinary result of a practically hopeless prognosis in five weeks, and apparently fatal result imminent in a few months. This actually happened. I removed first one breast and axillary contents, and the opposite one a few weeks later, patient dying in May, six months after the first invasion, with large metastatic masses in liver, both lungs, and pleuræ.

CASE II.—(The slowest I can remember.) Mrs. R. K., patient of Dr. C. P. Caldwell. Had slow-growing carcinoma of left breast. I estimated the time required for doubling at six months, basing this on history. This rate, plotted with the abscissæ representing six-months' intervals, gives a danger limit very slowly accelerated, and a fatal result years distant. Exactly this did occur. The breast and glands were removed by me, and patient had no recurrence for three years. I considered her cured.

Very slow redevelopment in the old breast scar and axilla then appeared, and patient eventually died of the cancer eight years after the first appearance.

I have tested this graphic method in a large number of cases by the past history, and a few by way of prophecy, and have every faith in its accuracy. By it we can exclude with fair accuracy all those cases which ought not to be operated upon. When the risk curve plotted by my law has risen to the upper half of the card, say to 90 or 100 per cent., it is useless to do other than palliative operations. There is no class of cases likely to discredit surgery more than those tumor operations so often done in which rapid recurrence takes place, and in which a subsequent review of the whole case shows patient's family and physician alike that the operation never really had a chance of succeeding. A careful application of this law will put us, at a middle stage of any case, almost in the position of one who has seen its whole course. I am certain that the first stages of any growth furnish the data for all the later stages, whether it be very slow or very rapid. Although each case has its own rate of progression, that rate once determined will accelerate uniformly, according to the law of squares.

I shall be very much interested to learn if these conclusions are not confirmed by the experience of other operators.